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Synthesis of (2R,6R)-Hydroxy-norketamine for Evaluation of Antidepressant Effects

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SYNTHESIS OF (2*R*,6*R*)-HYDROXY-NORKETAMINE FOR EVALUATION OF
ANTIDEPRESSANT EFFECTS

By
Savannah Fairley

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of
the requirements of the Sally McDonnell Barksdale Honors College.

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ABSTRACT

SAVANNAH FAIRLEY: Synthesis of (2R,6R)- Hydroxynorketamine for Evaluation
of Antidepressant Effects

(Under the direction of Dr. John Rimoldi)

Major Depressive Disorder, colloquially known as depression, is a devastating mental illness that affects a large portion of today's population. Following a drug side-effect that caused depression, the monoamine theory of depression was created, stating that depressive symptoms were caused by a decrease in concentrations of vital monoamine neurotransmitters at the synaptic cleft. Pharmaceutical remedies to combat depression were first introduced in the 1950s and to this date, most available drugs follow the monoamine theory. These drugs have a large loading dose lag time, numerous negative side effects, and still many patients do not experience relief from symptoms. In 2000, the Stress-neurogenic theory was proposed, suggesting depressive symptoms decreased neurogenesis and dendritic retraction, induced by excess cortisol from chronic stress. This new theory opened the door for further studies to be conducted on possible pharmacotherapies for MDD. Ketamine had shown some antidepressant effects, but was not a sufficient option due to the dissociative effects and history of abuse. Further studies were done to indicate that ketamine's antidepressant effects were caused by the metabolite (2R,6R)-hydroxynorketamine and that the mechanism of action seems to be NMDA receptor independent. The goal of this thesis was to construct an efficient complete synthesis pathway of (2R,6R)- hydroxynorketamine from commercially available chemicals. This was done by evaluating chemically and structurally similar reactions that had

been previously published to piece together a new synthesis of (2R,6R)-HNK. The product of this research will be sent to a partnering lab for further studies to be completed on the NMDA-independent and possibly AMPA receptor-dependent mechanism by which ketamine exhibits such promising antidepressant effects. Further understanding of this mechanism brings us one step closer to better future pharmacotherapies for MDD.

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LIST OF ABBREVIATIONS

MDD	Major depressive Disorder
HNK	Hydroxynorketamine
NMDA (R)	N-methyl-D-aspartate (receptor)
AMPA (R)	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (receptor)
MAOI	Monoamine oxidase inhibitors
SSRI	Selective serotonin reuptake inhibitor
SNRI	Selective norepinephrine reuptake inhibitors
CRH	Corticotrophin-releasing hormone
FDA	Food and Drug Administration
<i>In vivo</i>	Studies performed in a living organism
<i>In vitro</i>	Studies performed outside of a living organism
THF	Tetrahydrofuran
h	Hour
sat.	Saturated
NH ₄ Cl	Ammonium chloride
EtOAc	Ethyl acetate
Na ₂ SO ₄	Sodium sulfate
g	Gram
mL	Milliliter
p-TSA	p-Toluenesulfonic acid
NaHCO ₃	Sodium bicarbonate

m-CPBA	meta-Chloroperoxybenzoic acid
DCM	Dichloromethane
Aq.	Aqueous
PCC	Pyridine chlorochromate
RT	Room temperature
DMSO	Dimethyl sulfoxide
TPP	Triphenylphosphine
PCC	Pyridine chlorochromate

Introduction

Morbidity of Major Depressive Disorder

Major Depressive Disorder (MDD), more commonly known as depression, is a mental illness that is both chronic and debilitating, with a very high morbidity.¹ It is related to the natural emotion of sadness but does not remit once the external cause dissipates.² According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, MDD is characterized by an individual exhibiting at least five of the outlined depressive symptoms every day for a minimum of two weeks. These five symptoms may include: changes in appetite or weight, slowing of speech and action, disturbance of sleep schedule, strong feeling of worthlessness, lack of concentration, and suicidal ideation or actions.^{1,2} MDD has a life time prevalence of 14.4%, making it the most common mood disorder and the second most common mental illness in the United States, second to anxiety.¹ MDD has major socioeconomic consequences. Due to the combination of high morbidity rates and debilitating symptoms, MDD places a huge burden on the economy, contributing to \$83.1 billion in healthcare expenses in the United States (Year 2000 statistics).¹ On average, workers that suffer from severe depressive symptoms missed 13.7 more hours and cost their employers almost twice the healthcare expenses per year compared to other workers.¹

History of MDD Treatments and Theories

There are several FDA approved therapies indicated for the treatment of MDD; however, they have several key disadvantages that limit their effectiveness. In addition to unwanted side effects, the pharmaceutical drugs designed to treat MDD have a delayed onset of about 4-12 weeks before any measurable remission of symptoms are noticed.¹ Even after this time period, some patients never experience therapeutic relief, despite taking escalating doses. Those that fit into this category are considered to have treatment resistant depression and they account for 34-46% of all MDD diagnosed patients.¹

All of the FDA approved drugs indicated for the treatment of MDD are based on the monoamine theory of depression, which claims that MDD patients have low concentrations of serotonin, norepinephrine, and dopamine. Regardless of the therapeutic class, all aim to produce an increase in the concentration of these monoamine neurotransmitters at synaptic clefts. Evidence for the monoamine theory for depression was based on the drug reserpine, used in the 1950s to treat hypertensive vascular disease. Patients taking reserpine appeared to develop depression that remitted once the drug therapy was terminated. Studies confirmed the findings that reserpine inhibited a vesicular monoamine transporter and therefore lowered the concentrations of monoamines in the brain.¹ Another proof for the monoamine theory came from studies using monoamine oxidase inhibitors (MAOIs). MAOIs target and inhibit the enzyme monoamine oxidase, an enzyme responsible for the metabolism and clearance of neurotransmitter amines, resulting in the increase in concentration of these neurotransmitters. New therapeutics began to emerge with incremental advances in their

pharmacological mechanisms of action, but with the same end result: they were designed to increase concentrations of monoamine neurotransmitters at the neuronal synapses in order to alleviate depressive symptoms.¹

The next therapeutic class of drugs discovered after the MAOIs was the tricyclic inhibitors of norepinephrine and serotonin. Drugs in this class inhibit presynaptic norepinephrine and serotonin reuptake transporters as well as block postsynaptic adrenergic alpha receptors, postsynaptic muscarinic receptors, and postsynaptic histamine receptors.¹ The inhibition of these reuptake transporters for both norepinephrine and serotonin are cited to be the reason for the remission of symptoms, keeping in line with the monoamine theory of depression.

Major advances in treating depression was realized with the discovery of the selective serotonin reuptake inhibitors (SSRIs), which prevent the reuptake of serotonin resulting in clinically relevant increases in concentrations in the synaptic cleft and a higher concentration available to stimulate serotonin receptors at post-synaptic receptors. Logically, serotonin-norepinephrine inhibitors (SNRIs) were developed, therapeutics able to target both serotonin and norepinephrine reuptake receptors, but are more selective than the tricyclic drugs.

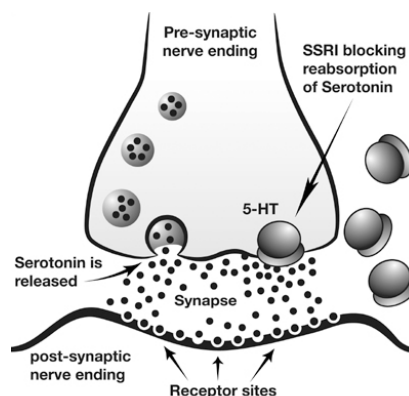


Figure I. Summarized selective serotonin reuptake inhibitor mechanism of action.⁶

These are just a few of the current MDD therapeutic classes that are FDA approved. Despite the variety in drug design and pharmacological mechanisms of actions, all of the current drugs for MDD require a loading dose lag time before they are effective. In addition, there are many treatment resistant MDD patients, which presents a need for further research.

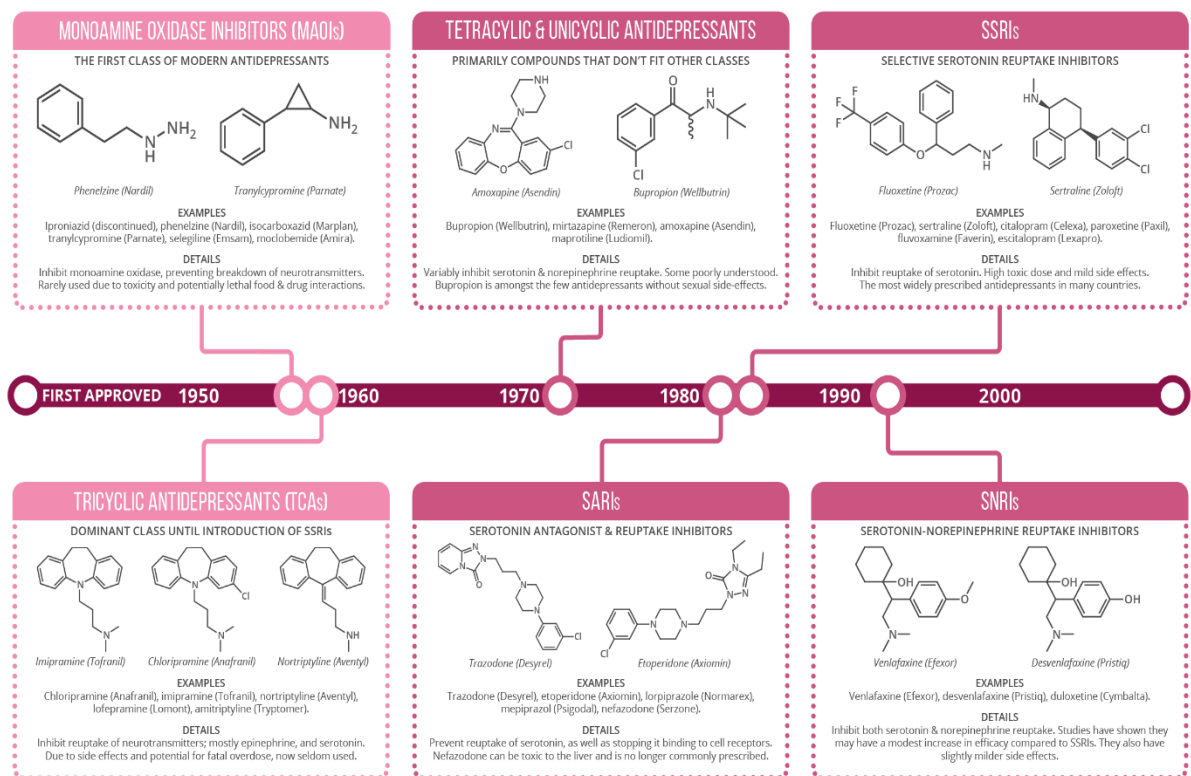


Figure II. Summary of Major Classes of Antidepressant Drugs.⁷

The Stress-Neurogenic Theory

Due to the large number of patients suffering from treatment resistant depression, there is support that depletion of monoamines may be a side effect of a much larger

neurobiological system in play.¹ The shortcomings of current MDD treatments led researchers to develop a new theory: the stress-neurogenic theory of depression. This theory states that unpredicted or chronic stress causes a larger amount of stress hormones to be produced, which in turn induce neuronal damage in areas of the brain, such as the amygdala and the hippocampus. Stress causes the release of corticotrophin-releasing hormone (CRH) from the hypothalamus that induces the release of corticotrophin from the pituitary gland.¹ Corticotrophin then activates the adrenal gland to release cortisol, which in excess causes decreased neurogenesis and dendritic retraction, leaving the neurons vulnerable to neurotoxicity and other metabolic changes.³ With this proposed theory, research efforts have been redirected to finding novel treatment pathways.

History of Ketamine and its Use as an Antidepressant

The FDA approved ketamine in 1970 as a short-term, noncompetitive NMDA receptor antagonist anesthetic in humans and animals, however it did not become widely used until the Vietnam War. Due to its light and controllable dissociative effects, ketamine's role in pediatric and veterinary medicine grew rapidly, as did its popularity as a recreational street drug. Recently, ketamine has been associated with antidepressant effects. The administration of sub-anesthetic doses of ketamine to MDD patients has shown strong and persistent efficacy, even within the first hour of the first dose.⁴ Although these findings bring great excitement to the field and to treatment resistant patients, this drug has limitations due to its hallucinogenic and dissociative effects as well as its abuse liability.⁴ For this reason, research efforts have focused on the identification of ketamine's direct antidepressant mechanism.

In vivo pharmacology studies have demonstrated that the N-demethylated metabolite norketamine exhibited approximately 50% of the anesthetic effects of ketamine, while hydroxynorketamine (HNK) had no anesthetic effects at all.⁵ This led researchers to hypothesize that norketamine was the active agent of ketamine and that its clinical effects came from N-methyl-D-aspartate receptor (NMDAR) inhibition.⁴ These studies led to the conclusion that hydroxynorketamine was therefore inactive.⁵

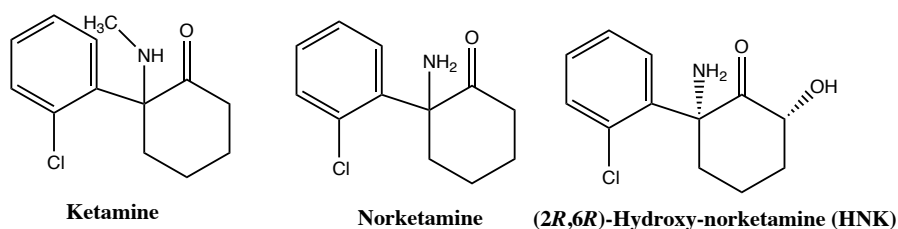


Figure III. Structure of Ketamine and two of its metabolites

More recent studies have investigated the concurrence of the antidepressant effects and the inhibition at the NMDA receptors, and have proved that other NDMA antagonists do not produce similar antidepressant effects.⁴ This data indicates that ketamine's antidepressant effects are likely due to an NMDAR inhibition- independent mechanism. Additional studies were performed to specifically test hydroxyl-norketamine's antidepressant effects. Ketamine was altered so that its metabolites, (2*S*,6*S*; 2*R*,6*R*)-hydroxynorketamine (HNK) would not form, however, the pharmacological effects of the molecule were not affected. Studies showed that without (2*S*,6*S* or 2*R*,6*R*)-HNK, antidepressant effects were not observed.⁴ It was confirmed that the (2*R*,6*R*)-HNK enantiomer exhibited the most efficacy in antidepressant trials, which also negates the NMDAR hypothesis since the *S*-HNK enantiomer is a more potent NMDAR inhibitor.⁴

During trials, a single dose of (2*R*,6*R*)-HNK exhibited antidepressant effects similar to those of ketamine; fast and persistent remission of symptoms.⁴

To further assess the mechanism of action of (2*R*,6*R*)-HNK, researchers used tagged molecules bound at NMDA receptors to measure the metabolites antagonistic effect. In the vitro studies, (2*R*,6*R*)-HNK did not displace the tagged molecules, therefore the antidepressant effects of (2*R*,6*R*)-HNK are not associated with the NMDA receptors.⁴ However, the metabolite did show an increase in α - amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated excitatory post-synaptic potentials as well as an increase in the frequency and amplitude of AMPAR-mediated excitatory postsynaptic currents.⁴ Studies confirmed the role of AMPA receptor activation on antidepressant effects. Mice were pretreated with an AMPAR antagonist prior to (2*R*,6*R*)-HNK injections, resulting in no noticeable antidepressant effects. This indicated that activation of the AMPA receptors is required for (2*R*,6*R*)-HNK antidepressant mechanism of action.⁴

Ketamine's use as an antidepressant drug is limited due to the abuse liability and the sensory, motor, and dissociative effects it causes. Studies prove that (2*R*,6*R*)-HNK did not produce any sizable changes in motor and sensory process, even at high doses.⁴ Due to the lack of side effects and the NMDAR- independent mechanism of action; (2*R*,6*R*)-HNK is a favorable molecule for the development of new, fast-acting antidepressant drug treatments. The goal of this study was to develop a novel and efficient complete synthesis of (2*R*,6*R*)-hydroxynorketamine to be used for in vivo physiological studies.

Results and Discussion

As a result of several milestone publications, it is now well-established that the ketamine metabolite, (2*R*,6*R*)-hydroxynorketamine is a major contributor to ketamine's antidepressant effects. The specific aim of the thesis research outlined was to design and execute a simple and cost-effective synthesis of (2*R*,6*R*)-hydroxynorketamine (HNK). This compound will be tested in the laboratory of Dr. Kenneth Sufka at the University of Mississippi using an innovative and unique in vivo antidepressant screening model. This laboratory has developed and continues to validate an avian social-separation stress procedure that simulates several characteristics of treatment-resistant depression (TRD).¹³ Indeed, it is the only assay that meets the FDA definition of TRD, which is the failure to respond to two classes of FDA-approved antidepressants.^{14,15} If this model successfully screens HNK, this may very well open the door to the development and screening of a broad library of compounds related to HNK that may prove highly efficacious in TRD populations.

The design of synthetic pathways for this project began in Spring 2017; at this time there were no synthetic reports published for (2*R*,6*R*)-hydroxynorketamine. Since then, two total synthesis have been reported. Researchers at the Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, NIH reported the synthesis of (2*R*,6*R*)-hydroxynorketamine from (*R*)-ketamine (prepared in 6 steps from cyclohexanone) using a Rubottom oxidation as the key step in the

synthesis, providing a 72% yield and an excellent diastereomeric ratio to install the α -keto-alcohol with the desired stereochemistry (Figure 4).⁸

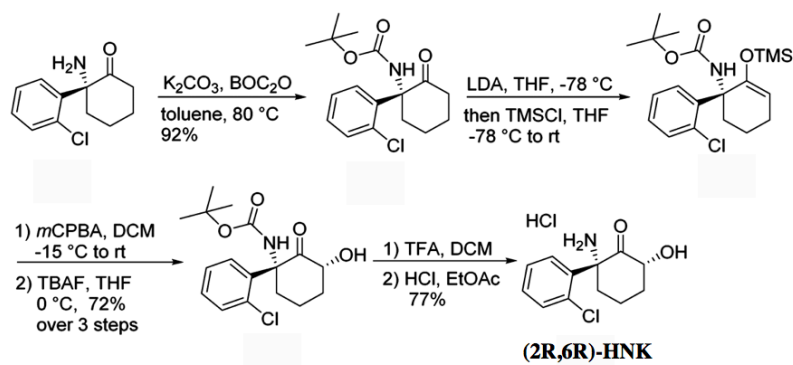


Figure IV. Morris Synthesis, NIDA-NIH, 2017.⁸

A second synthesis of (2R,6R)-hydroxynorketamine was reported by Corey, who utilized a mechanistically-guided catalyst selection (manganese) for the initial olefin epoxidation step, and a novel O \rightarrow N displacement with retention of configuration through the use of Al- or Ti-based azides to promote epoxide activation and internal *cis* delivery of azide (Figure 5). Although novel and elegant, the synthesis is expensive due principally to the use of a chiral Mn catalyst and non-commercially available reagents.⁹

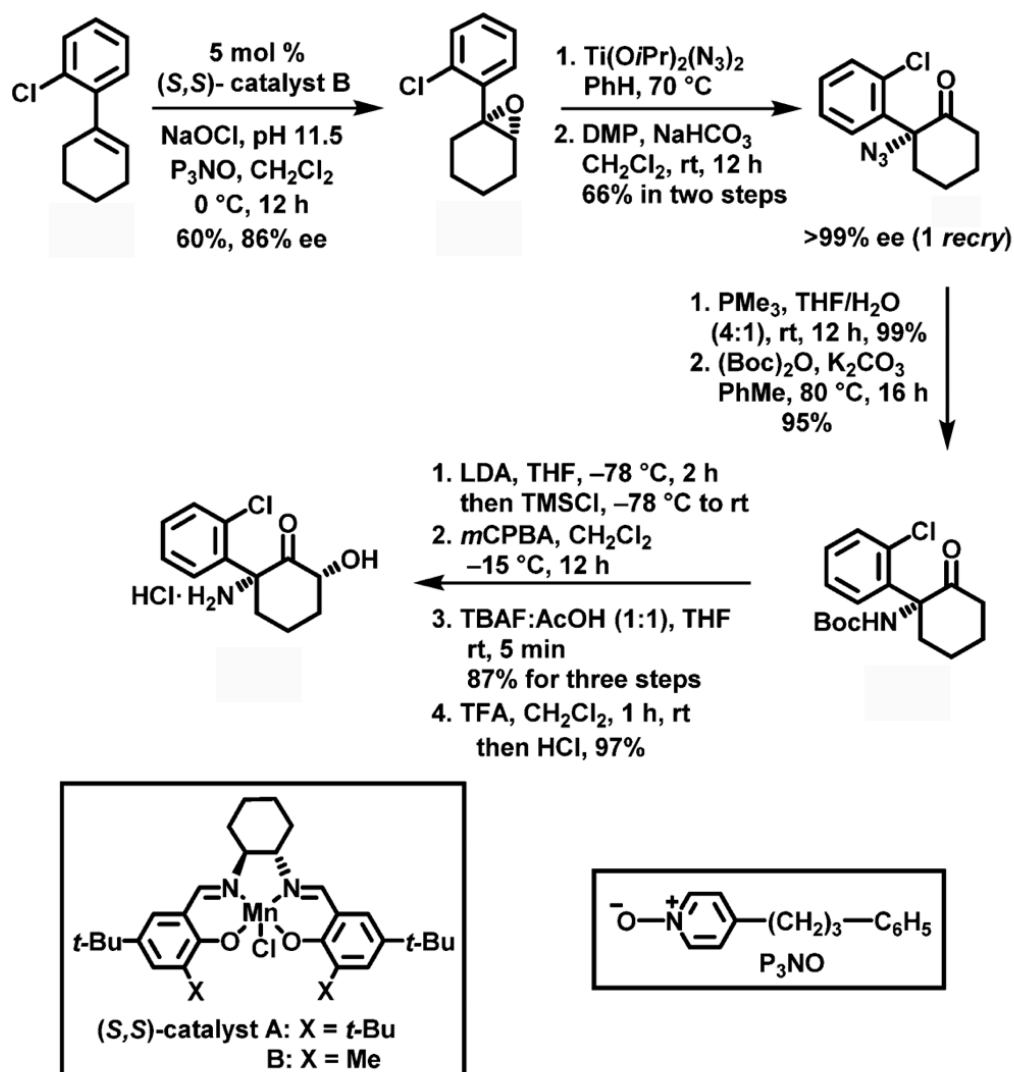


Figure V. Corey Synthesis, Harvard, 2017⁹

One theme emerges from the analysis of the reported syntheses: they both invoke the synthesis of (*R*)-norketamine (or its protected version) followed by a late-stage oxidation. Although these two papers described the successful synthesis of

(2*R*,6*R*)-HNK, the goal of this thesis research was to design a new and efficient synthesis, cost-effective and scalable. Our synthesis began with easily accessible and commercially available starting materials, with the initial aim of synthesizing gram scale racemic norketamine. The racemic material would then be subject to diastereomeric salt formation for enantiomer resolution. Figure VI illustrates the synthetic pathways employed.

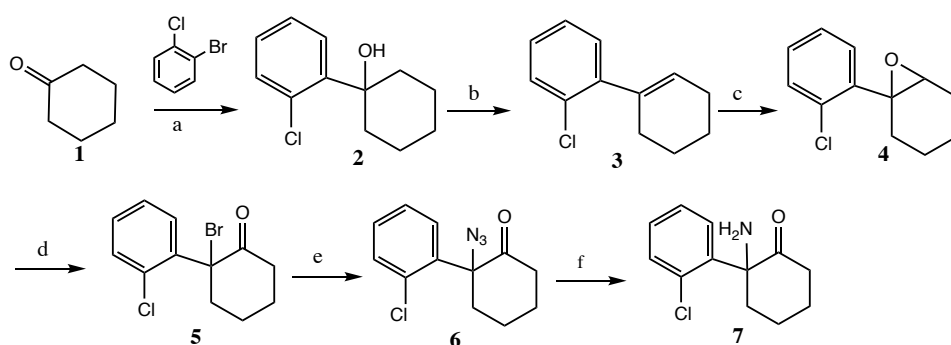


Figure VI: Synthesis of (*rac*)-Norketamine (7a). Experimental Conditions: a.) Mg, THF, chlorobromobenzene, **1**, (40%). b.) PTSA, toluene, reflux (92%); c.) NaHCO₃ (15mL) NaHCO₃, m-CPBA, (80%); d.) HBr (aq.), PCC, CHCl₃ (39%). e.) DMSO, NaN₃ (82%). f.) PPh₃, water, reflux.

The synthesis of racemic norketamine (**7**) was initially reported by Sulake et al. We adopted this methodology, apart from the use of deuterium labeled reagents and made some improvements to the reported methods. Commercially available bromo-chlorobenzene was converted to a Grignard reagent and reacted with cyclohexanone (**1**) to yield the tertiary alcohol (**2**), which was subject to a dehydration step affording olefin (**3**) in good yields. The low yielding Grignard reaction may be a consequence of moisture present during the reaction. This step was not optimized. The stage was set for an epoxidation reaction of **3** with *m*-CPBA; initial experiment confirmed the findings that the epoxide generated was relatively unstable. A change in the R_f value was noticed after the compound had been stored for a week at 0°C. Therefore, the epoxidation was performed using a biphasic solution of dichloromethane and 5% sodium bicarbonate to eliminate the potential for rearrangement products, resulting in epoxide **4**.⁸ The epoxide ring was then subjected to regioselective epoxide ring-opening reaction with HBr followed by a PCC-mediated oxidation to yield the targeted brominated ketone (**5**) in a one-pot reaction. Compound **5** was then treated with sodium azide to afford product **6**. A Staudinger reaction was employed for the reduction of azide (**6**) to generate (rac)-norketamine **7**. The mechanism of this reaction involves the reaction of triphenylphosphine with the terminal nitrogen of the azide, followed by a facile rearrangement, leading to the intermediate iminophosphorane. Water attack on this intermediate leads to a hydrolytic reaction generating amine and triphenylphosphine oxide as the by-product (which is not easily separated from the product).

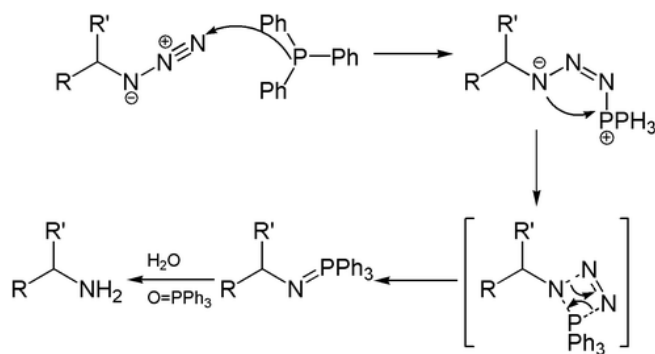


Figure VII: Proposed Staudinger Reaction Mechanism.¹⁰

A quantity of (rac)-norketamine (**7**) has been successfully synthesized, and prior to enantiomeric resolution using a chiral salt, initial experiments were conducted to explore a simple and cost effective late stage oxidation reaction. Reaction of **7** with methychloroformate afforded carbamate **8**. Reactions are in progress to explore the scope and utility of a new and simple oxidation reaction that has been recently reported, namely the DMSO-Iodine promoted direct oxidation of carbonyl derivatives. The simple and readily available iodine or NBS is used as catalyst, and DMSO acts as the oxidant, oxygen source, and solvent.¹¹ The interpretation of the mechanism is that the oxidation should proceed from the less hindered face of the cyclohexone ring, and facial selectivity should be improved by the directing effects of the amine carbamate group. If this reaction proves successful, the remaining steps are to conduct a deprotection reaction of the carbamate (KOH hydrolysis), and resolution of the major cis-disasteromer.

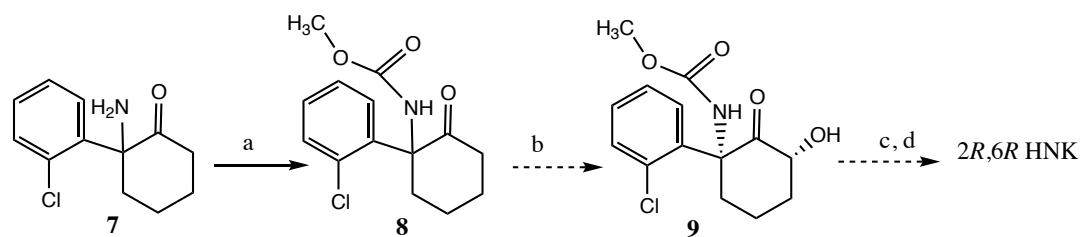


Figure VIII: Final Protection-Oxidation-Deprotection Steps.

Materials and Methods

General Methods

All reactions were completed using commercially available solvents and reagents. Every reaction was done under standard anhydrous conditions, unless otherwise stated. Standard anhydrous conditions meaning that oven-dried glassware was purged with argon in order to remove all moisture and anhydrous “dry” solvents were used. All reactions were monitored with thin layer chromatography (TLC) to check amount of starting material leftover and for product formation.

Phosphomolybdic acid was used to stain all TLC plates, as it had the best results for these compounds. Low-resolution mass spectroscopy was obtained at each step to confirm that the product molecular weight was present. For all Nuclear Magnetic Resonance (NMR) data, a Bruker 400 MHz Avance NMR spectrometer was used, and all raw data was processed with MestReNova software.

(2) 1-(2-chlorophenyl)cyclohexan-1-ol

A Grignard reagent was created by adding a solution of o-bromochlorobenzene (2.2 mL) in dry THF (22 mL) drop wise to a mixture of Mg (0.5 g) and I₂ (cat.) in anhydrous THF (8 mL) at 10-15 °C over 0.5 h. A solution of cyclohexanone (2.29 mL) in dry THF (15 mL) was added to the Grignard reagent at 0°C and stirred for 1 h. The temperature was then slowly increased to 20-25°C and the reaction continued to stir for 15 h. The mixture was quenched with sat. NH₄Cl,

added dropwise. The mixture was then extracted with an equal amount of EtOAc and the organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to give a yellow oil. The product was purified by silica gel column chromatography (hexane/EtOAc, 10:1). This reaction yielded 1.59 g (40%) of **2**. (1H NMR (400 MHz, Chloroform-D) δ 7.72 – 7.45 (m, 1H), 7.40 – 6.91 (m, 3H), 2.49 (d, J = 22.7 Hz, 1H), 2.27 – 2.02 (m, 2H), 2.01 – 1.42 (m, 7H), 1.41 – 1.05 (m, 1H), 13C NMR (101 MHz, CDCl₃) δ 144.96, 131.67, 128.15, 127.25, 127.01, 77.35, 77.04, 76.72, 73.91, 35.63, 25.34, 21.94.

(3) 1-(2-chlorophenyl)cyclohexene

Compound **2** (1.59 g) was dissolved in toluene (32 mL) and dehydrated by refluxing with PTSA (75 mg) and using azeotropic distillation by way of a Dean-Stark condenser. The mixture refluxed for 3 hours at 160°C and then left to stir at room temperature for 12h. The reaction mixture was washed with saturated NaHCO₃ and water. The organic layer was dried over Na₂SO₄ and then concentrated under pressure to give 1.34 g (92%) as a colorless oil. (1H NMR (400 MHz, Chloroform-D) δ 7.43 – 7.24 (m, 2H), 7.26 – 7.14 (m, 4H), 5.70 (s, 1H), 5.65 (s, 1H), 2.33 (td, J = 5.9, 2.8 Hz, 3H), 2.22 (tt, J = 7.1, 3.6 Hz, 3H), 2.18 (s, 3H), 1.85 – 1.69 (m, 7H), 13C NMR (101 MHz, CDCl₃) δ 143.48, 137.67, 132.45, 130.17, 129.47, 127.71, 127.25, 126.55, 100.00, 77.35, 77.03, 76.71, 29.15, 25.40, 22.88, 22.0

(4) 1-(2-chlorophenyl)-7-oxabicyclo[4.1.0]heptane

A solution of 5% NaHCO₃ (15 mL) was added to m-CPBA (1.48 g, 8.6 mmol) in DCM (15 mL) and stirred and 0°C. Compound 3 was dissolved in DCM (3 mL) and added dropwise to this solution, which was then stirred for 15 h at room temperature. The reaction mixture was separated using H₂O, dried over Na₂SO₄. The compound was purified with silica gel chromatography (hexane/EtOAc, 10:1) to yield 1.32 g (80%) colorless oil. (1H NMR (400 MHz, Chloroform-D) δ 7.46 (dd, *J*=7.2, 2.0 Hz, 1H), 7.43 – 7.31 (m, 1H), 7.30 – 7.17 (m, 2H), 2.08 (ddq, *J*= 30.1, 14.7, 8.7, 7.3 Hz, 3H), 1.68 – 1.39 (m, 3H), ¹³C NMR (101 MHz, CDCl₃) δ 141.23, 132.10, 128.96, 128.53, 127.99, 126.78, 100.00, 77.35, 77.04, 76.72, 60.58, 60.02, 29.43, 24.78, 20.31, 18.80).

(5) 2-bromo-2-(2-chlorophenyl)cyclohexanone

Compound 4 (1.32 g, 6.35 mmol) was dissolved in chloroform (30 mL) and stirred with 48% aq. hydrobromic acid (17 mL) at 0°C for 0.5 h. The aqueous layer was separated and then extracted three times with chloroform (3x 10 mL). The combined organic layer was then washed with equal amounts of sat. aq. NaHCO₃. The solvent was evaporated off and the residue was redissolved in DCM (20 mL). Pyridinium chlorochromate was added to this solution and stirred at RT for 13h. The reaction mixture was filtered through celite and then washed with HCl and water. Organic layer was washed with water and brine and then dried over Na₂SO₄. The product was concentrated under pressure and then purified using silica gel chromatography (hexane/EtOAc, 10:1) to yield 700 mg (39%) of a colorless oil. (1H

NMR (400 MHz, Chloroform-D) δ 7.99 (d, J = 7.4 Hz, 1H), 7.37 (ddq, J = 24.3, 16.3, 8.8, 8.1 Hz, 4H), 3.09 (dd, J = 15.3, 8.4 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.65 (d, J = 15.4 Hz, 1H), 2.41 (d, J = 15.1 Hz, 1H), 1.95 – 1.89 (m, 1H), ^{13}C NMR (101 MHz, CDCl_3) δ 201.43, 170.66, 137.86, 131.89, 131.34, 130.96, 129.71, 127.37, 77.35, 77.03, 76.71, 73.55, 43.09, 37.38, 25.56, 22.63.

(6) 2-azido-2-(2-chlorophenyl) cyclohexanone

DMSO (3.67mL) was used to create a solution of compound **5** (700mg). NaN_3 (468mg) was added to the DMSO solution and stirred at 25°C for 5 h. The reaction mixture was combined with water (10mL) and extracted with ethyl acetate (10mL x 3). The organic layer was then washed with water and then dried over Na_2SO_4 . The compound was purified using silica gel chromatography (hexane/EtOAc, 10:1) and gave 500mg (82%) as a colorless oil. (^1H NMR (400 MHz, Chloroform-d) δ 7.47 7.26 (m, 1H), 2.75 – 2.47 (m, 1H), 2.07 – 1.95 (m, 1H), 1.86 (dddd, J = 27.6, 18.9, 14.0, 8.3, 4.3 Hz, 1H), ^{13}C NMR (101 MHz, CDCl_3) δ 203.26, 137.13, 132.46, 131.35, 129.67, 127.95, 127.35, 77.34, 77.03, 76.71, 74.05, 38.86, 37.58, 25.41, 21.31).

(7) 2-amino-2-(2-chlorophenyl) cyclohexanone

Triphenylphosphine (600mg) was added to a solution of THF (10mL) and compound **6** (500mg). This mixture refluxed for 12 h at 65°C, water (0.15mL) was added and the mixture continued to reflux for 3 h. The solvent was removed under

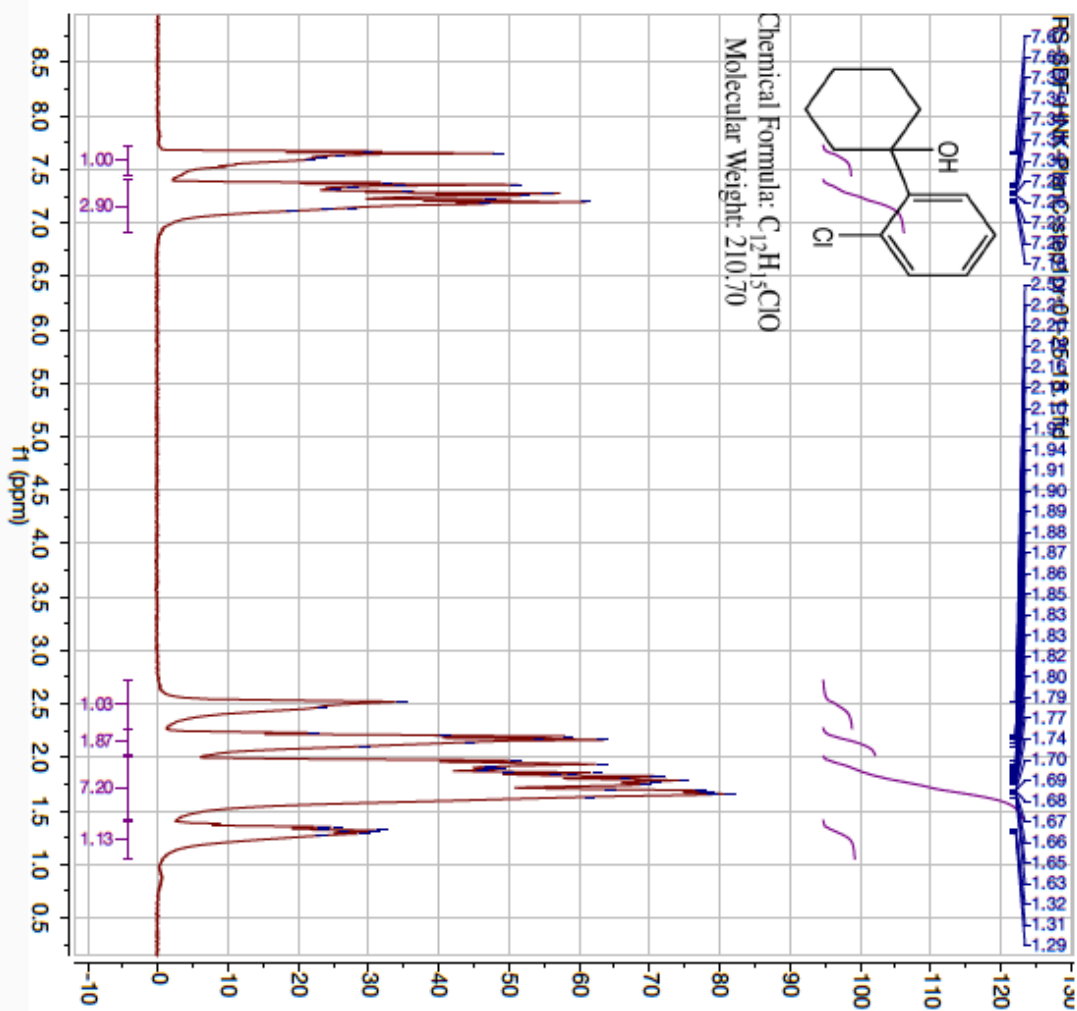
pressure and the compound was diluted with DCM (7mL) and 1M HCl (7mL). Sat. NaHCO_3 was used to basify the aqueous layer, which was then extracted with DCM (3 x 10mL). The organic layer was washed with water and dried over Na_2SO_4 . The compound was concentrated under pressure to yield a colorless oil. (^1H NMR (400 MHz, Chloroform- d) δ 7.80 – 7.73 (m, 3H), 7.72 – 7.62 (m, 25H), 7.59 – 7.51 (m, 16H), 7.51 – 7.40 (m, 28H), 7.40 – 7.35 (m, 4H), 7.35 – 7.27 (m, 4H), 3.32 (s, 1H), 2.62 – 2.57 (m, 1H), 2.02 (s, 1H), 1.84 – 1.74 (m, 4H), 1.26 (s, 4H), ^{13}C NMR (101 MHz, CDCl_3) δ 170.66, 132.96, 132.14, 132.04, 131.99, 131.96, 131.92, 131.20, 129.95, 128.58, 128.55, 128.46, 127.51, 77.40, 77.08, 76.76, 38.92, 29.70, 22.00).

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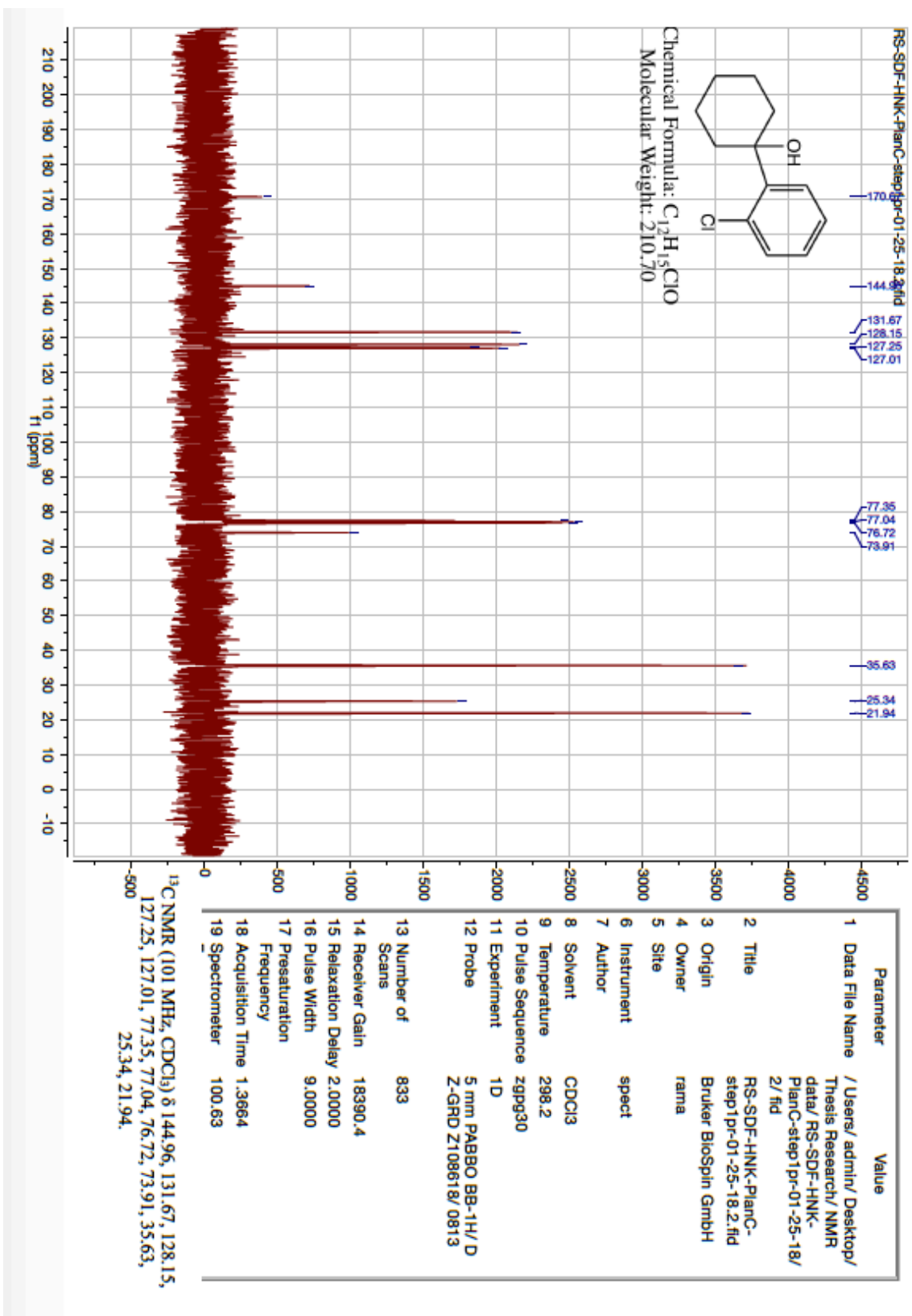
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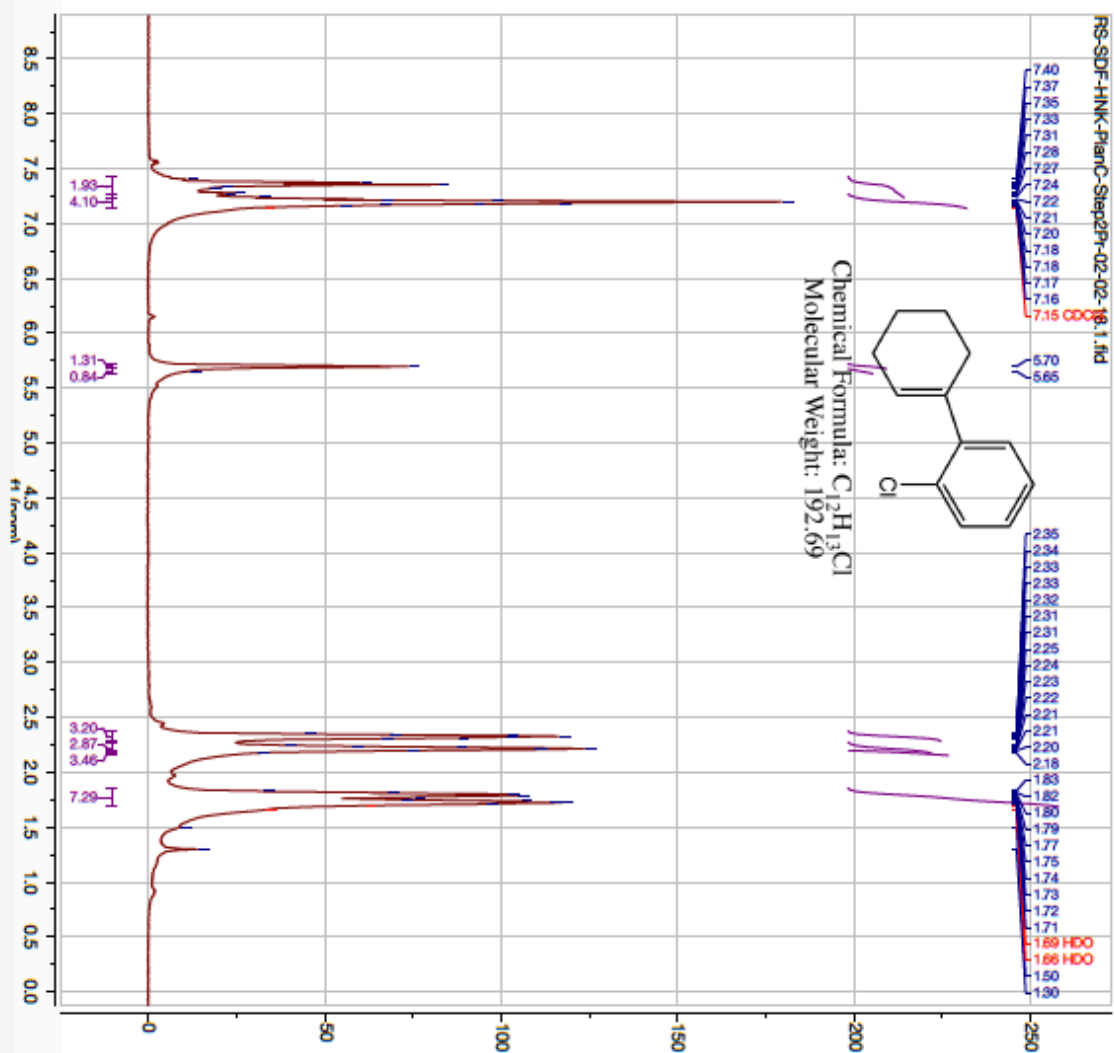
APPENDIX



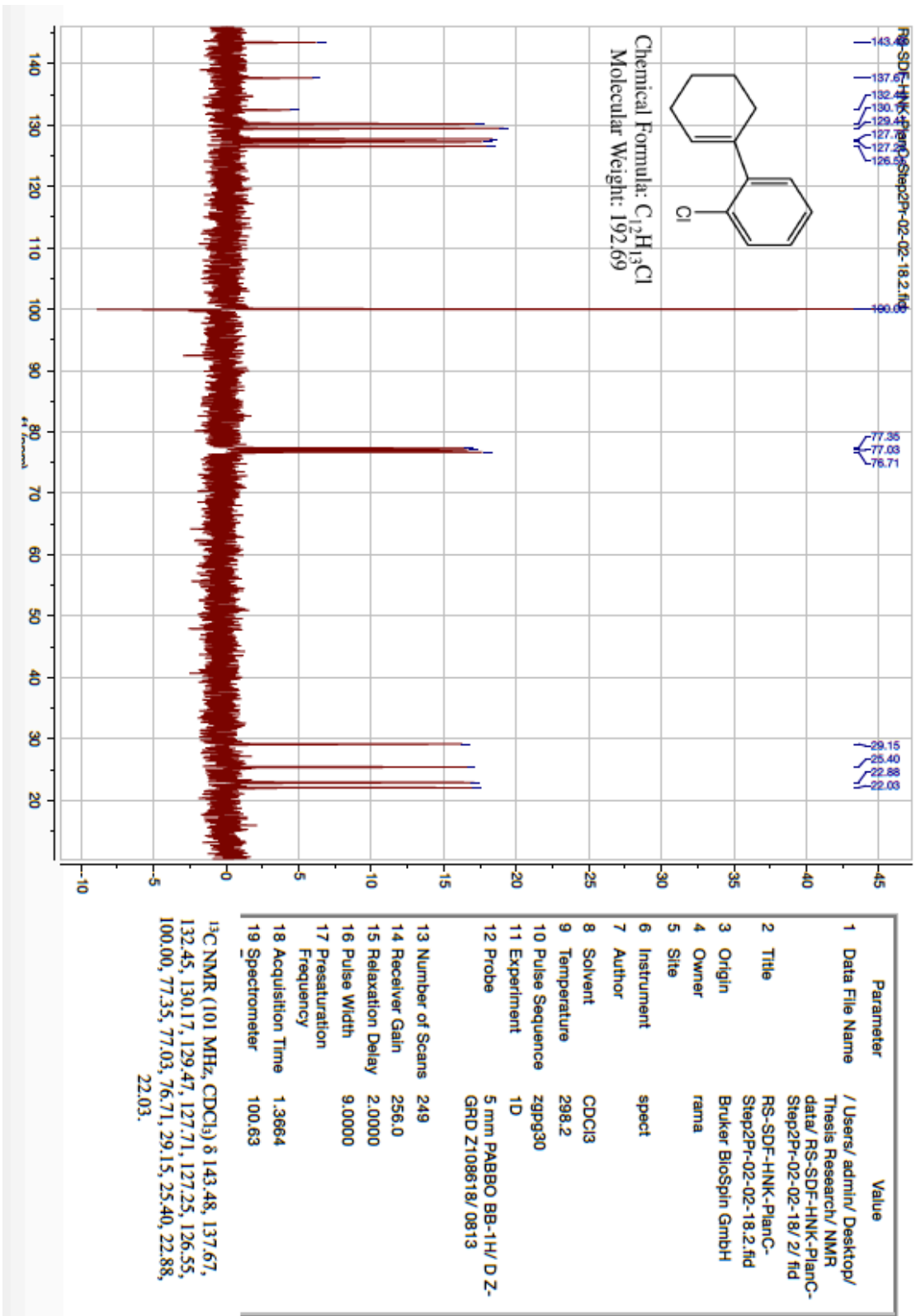
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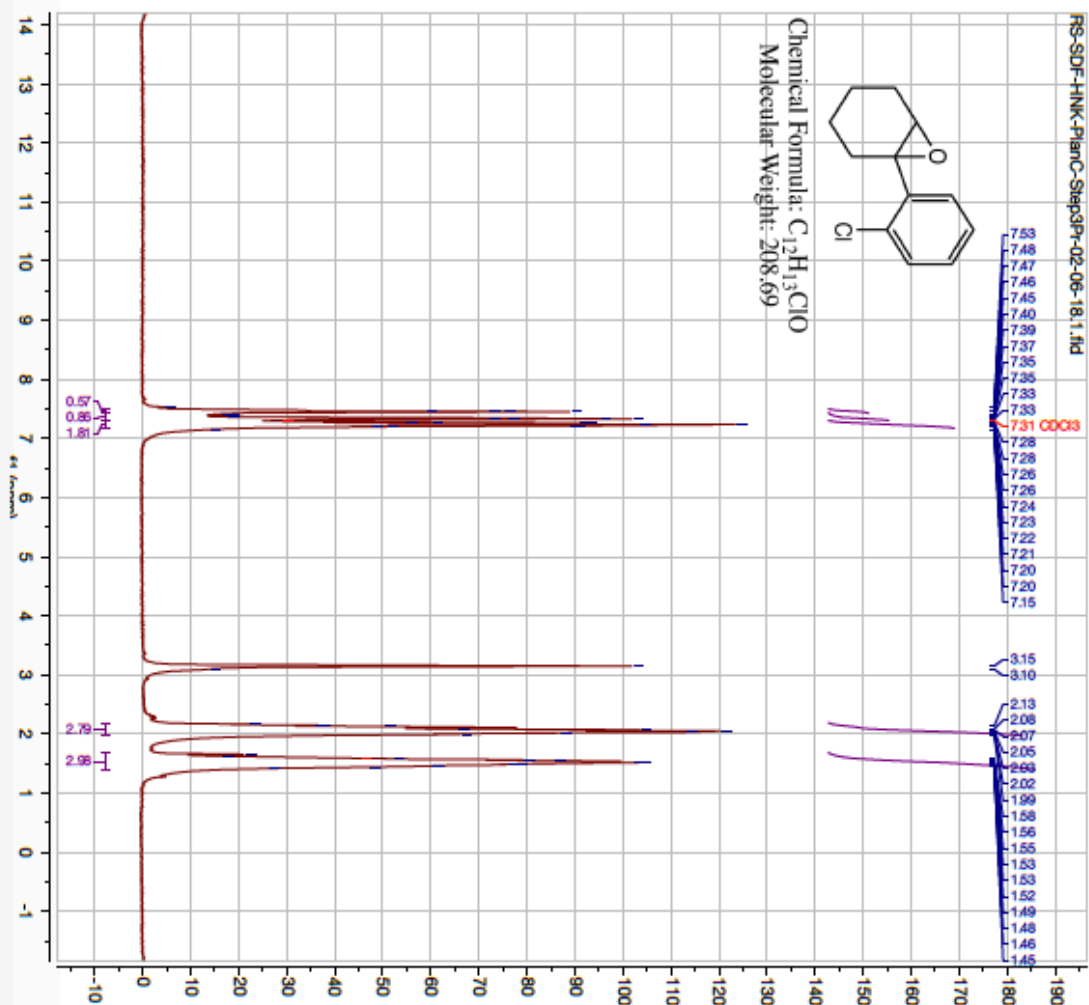
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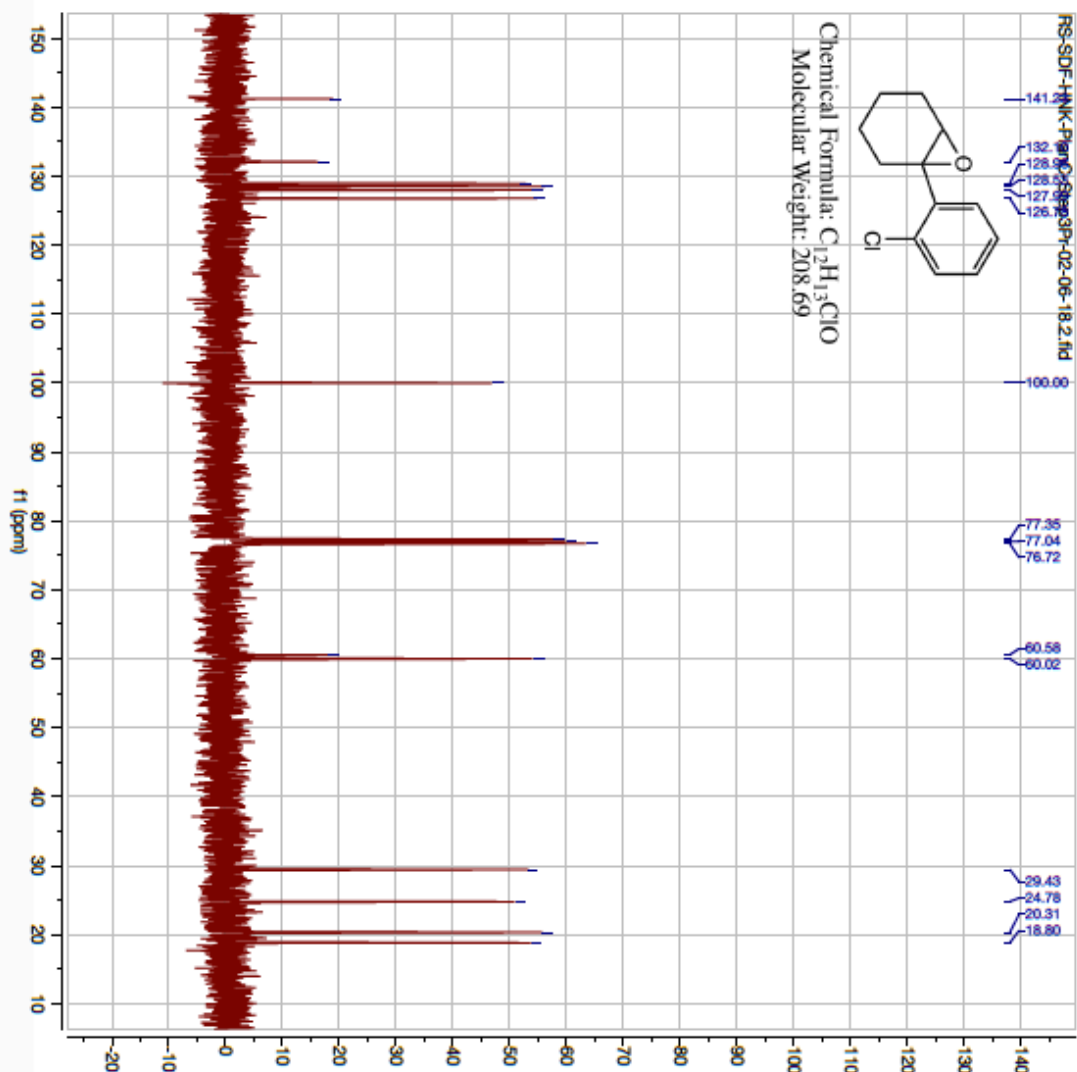


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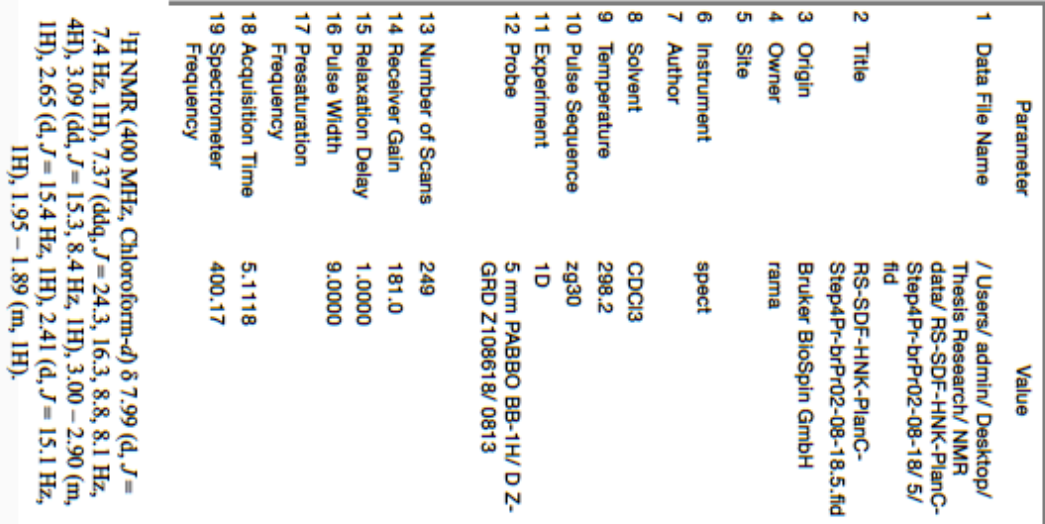


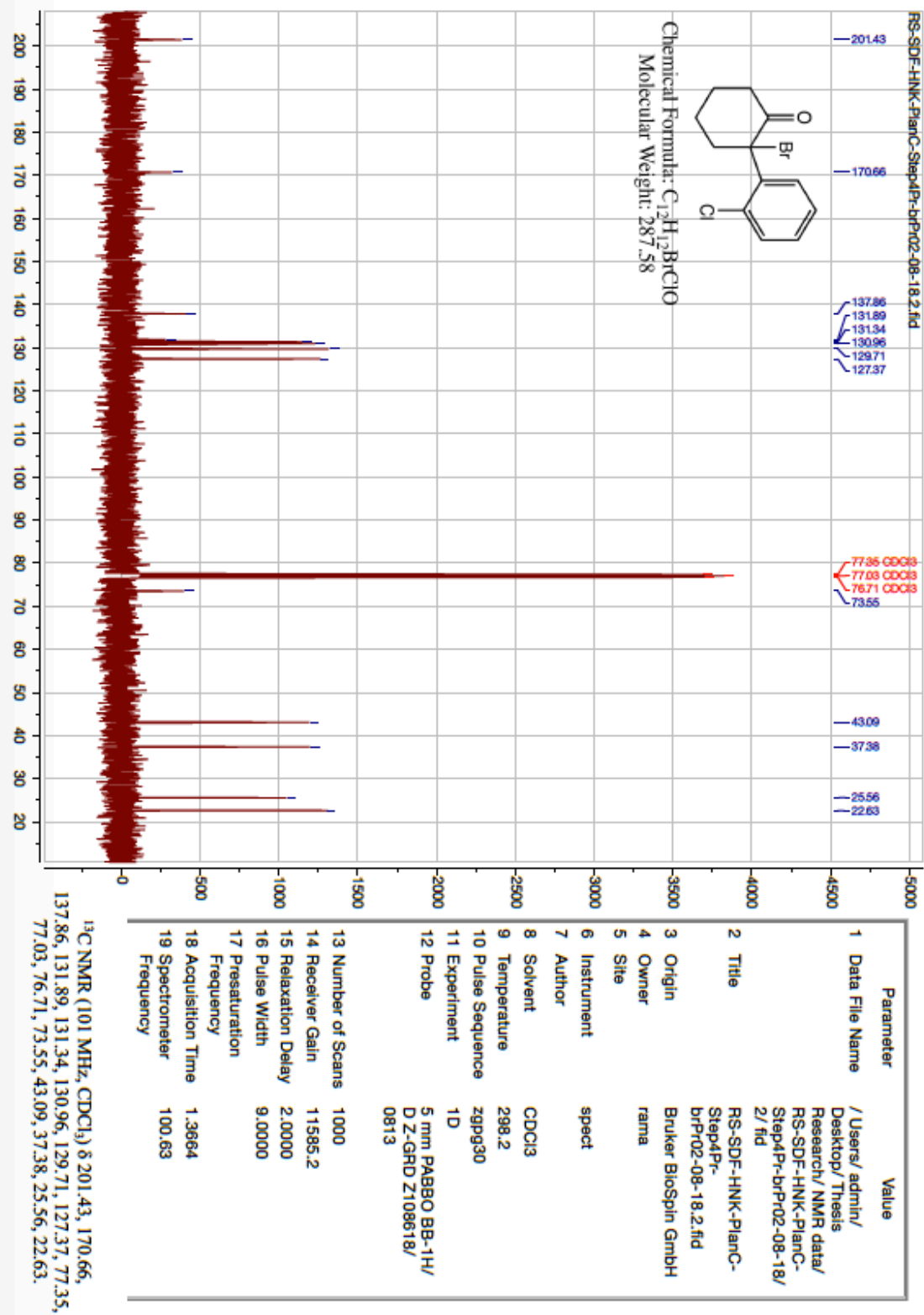
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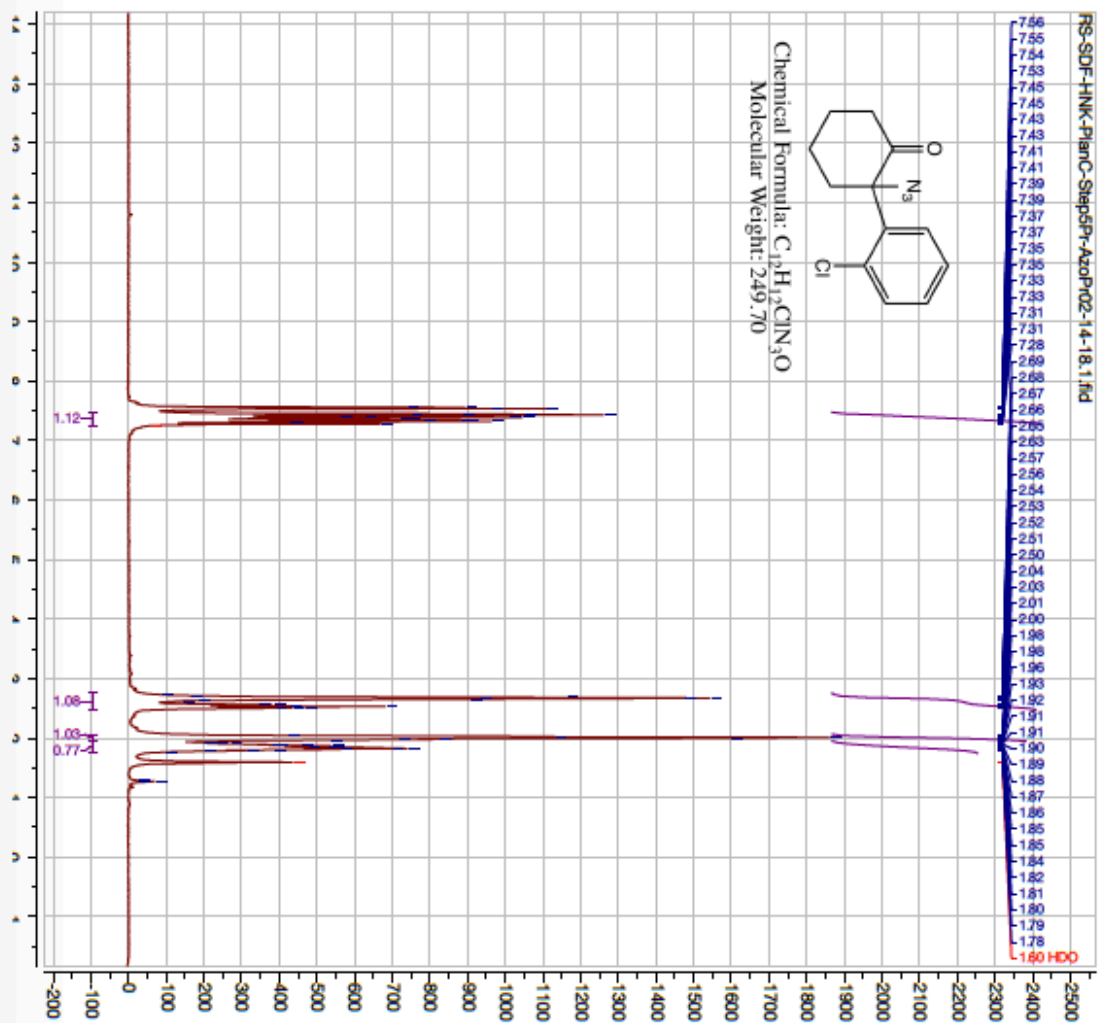


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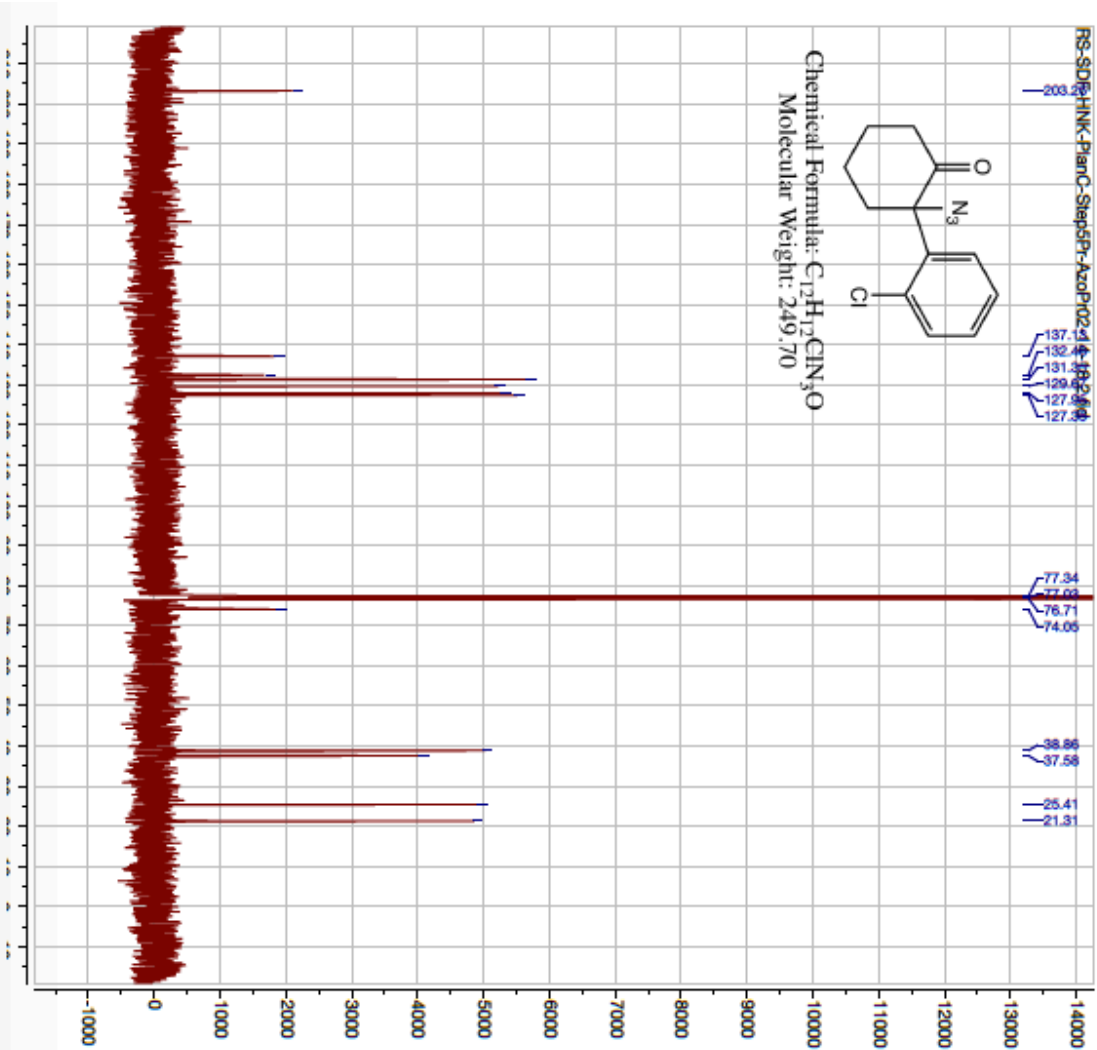






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